REMARKS

Claims 72-100 are pending in the above-identified application. Claims 72, 81, 84, 97-89, 91-93 and 95-100 are rejected as discussed below. Claims 73-80, 83, 85, 86 , 90 and 94 are objected to. Claims 73, 78, 81, 83, 84, 88, 90, 91 and 94 are amended to depend from Claim 93. Claim 81 is also amended to include epilepsy, multiple sclerosis, Down's Syndrome, nerve deafness and Meniere's disease among the injuries and dysfunctions recited in the claim. Support for the amendments can be found in the specification and claims as originally filed. In addition, Claim 91 is amended to recite "wherein the receptor is exposed to the antibody in an amount of from 1 μg/kg to about 100 mg/kg per day." The amendment is made to provide proper antecedent basis for the claim. No new matter is added by way of any of these amendments. Claims 72, 74-77, 79, 80, 87 and 99 are cancelled without prejudice. Upon entry of the amendment and response, Claims 73, 78, 81-86, 88-98 and 100 will be pending and are presented for further examination.

Objections to the Claims

Claims 73-80, 83, 85, 86, 90 and 94 are objected to for depending from cancelled claims. Claims 72, 74-77, 79, and 80 are cancelled without prejudice. Claims 73, 78, 83, 90 and 94 are amended to depend from Claim 93 for the reasons discussed below. Claims 85 and 86 depend from Claim 83, which is amended to depend from Claim 93. In view of the amended claims, Applicants respectfully request withdrawal of the objections to the claims.

Rejection of Claims Under 35 U.S.C. §112. First Paragraph, Enablement

Claims 72, 81, 82, 84, 87-89, 91-93 and 95-100 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement, as applied to Claims 1-5, 7, 10-17, 33-37, 40-42 and 45. The Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully disagree.

"To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation'.... Nothing

more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. M.P.E.P. § 2164.08 (citing *In re Buchner*, 929 F.2d 1557 (Fed. Cir. 1993)). Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *See Hybritech Inc. v. Mononoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

The Claims

The claims relate to methods for inhibiting the binding of a pro-neurotrophin to a receptor of the Vps10p-domain receptor family by exposing the receptor to an antibody that also binds the receptor and is thus able to compete with the pro-neurotrophin for binding. Accordingly, independent Claim 93 recites a method for inhibiting the binding of a pro-neurotrophin to a receptor of the Vps10p-domain receptor family in an animal, which comprises exposing said receptor to an inhibitorily effective amount of an antibody which binds such a receptor, and thereby inhibits the binding of a pro-neurotrophin to said receptor. Claims 73, 78, 81-86, 8892, 94-98 and 100 depend from Claim 93 and thus contain all the features thereof as well as additional features recited in the claims. Claims 72, 74-77, 79, 80, 87 and 99 are cancelled without prejudice.

The Claims Satisfy the Enablement Requirement

In rejecting the claims, the Examiner asserts that "[t]here is no evidence of record that provides a nexus between the pro-apoptotic effect of pro-neurotrophins and the etiology, pathology and symptomology of an injury or dysfunction of the central or peripheral nervous system." The Examiner also argues that the instant specification does not disclose any direct connection between Vps10p-domain receptors and neurotrophin or pro-neurotrophin activity, and therefore is not found to be enabled for the method as claimed. Applicants respectfully disagree.

As discussed above, the claims are directed to methods for inhibiting the binding of a pro-neurotrophin to a receptor of the Vps10p by exposing the receptor to antibodies that also

bind the receptor. Furthermore, as the Examiner noted in the Final Office Action, the standard of an enabling disclosure is "the ability to make and use with a reasonable expectation of success." Thus, Applicants need only show a reasonable expectation of success for antibody binding to the receptor, rather than a connection between pro-neurotrophins and injury or dysfunction of the central or peripheral nervous system, in order to satisfy the enablement requirement. The specification as filed, in particular the Figures accompanying the specification, disclose binding of neurotrophins to Vps10p-domain receptors. The specification also provides information, including sequence information, about exemplary Vps10p receptors, which is sufficient to those of skill in the art to make and use antibodies that bind the receptors. Methods of making and screening antibodies are performed routinely by those of skill in the art and accordingly do not need to be specifically disclosed in the instant application in order to carry out the claimed embodiments.

However, notwithstanding the factors necessary for satisfying the enablement requirement, Applicants also note that there is ample evidence in the art linking the apoptosis with injury or dysfunction of the central or peripheral nervous system. For example, apoptosis is associated with Alzheimer's Disease (Podleniy *et al.* 2006. *Am J Pathol* 169:119-131), Parkinson's Disease (Camins *et al.* 2008. *Methods Find Exp Clin Pharmacol* 30:43-54), Huntington's chorea (Gil and Rego. 2008. *Eur J Neurosci* 27:2803-2020), depression (Lucassen *et al.* 2006. *CNS Neurol Disord Drug Targets* 5:531-546; Bachis *et al.* 2008. *Neurosci Lett* 442:104-108; Kosten *et al.* 2008. *Neuropsychopharmacology* 33:1545-1548), multiple sclerosis (Hebb *et al.* 2008. *Curt Drug Discov Technol* 5:75-77; Das *et al.* 2008. *CNS Neurol Disord Drug Targets* 7:313-320), Down's Syndrome (Busciglio and Yankner. 1995. *Nature* 378:776-779; Enigdawork and Lubec. 2003. *J Neurochem* 84:895-904), Meniere's Disease (Semaan *et al.* 2005. *Curt Opin Otolaryngol Head Neck Surg* 13:301-307), schizophrenia (2007. *Czernansky Scientific World Journal* 7:135-143; Benes. 2006. *Prog Brain Res* 158:153-172), virus-induced neuronal cell death (Stoica *et al.* 2008. *Brain Res* 1208:204-216) and bipolar disorder (Benes. *supra*). Pro-neurotrophin-linked apoptosis is linked with central or peripheral nervous system injury or dysfunction such as, but not limited to, stroke (inventor's unpublished data; Bruno and, Cuello. 2006. *PNAS* 103:6735-6740; Miles and Knuckey. 1998. *J Clin Neurosci* 5:125-145); ALS (Pehar *et al.* 2006. *Eur J Neurosci* 26:1575-1580; Domeniconi *et al.*

2007. *Mol Cell Neurosci* 34:271-279), mania (Politi *et al.* 2008. *Arch Med Res* 39:242-245; Post *et al.* 2007. *J Psychiatric Res* 41:989-990; Martinowich *et al.* 2007. *Nat Neurosci* 10:1089-1093; Chen *et al.* 2005. *J Neurosci* 25:6156-6166; Egan *et al.* 2003, *Cell* 112:257-269; Chen *et al.* 2006. *Science* 314:140-143; Teng *et al.*. 2005, 1 *Neurosci* 25:5455-5463; Chuang. 2006. *Ann NY Acad Sci* 1053:241-245), epilepsy (Humpel *et al.* 1993.1 *Neurosci Res* 35:419-427; Volosin *et al.* 2006.1 *Neurosci* 26:7756-7766; Unsain *et al.* 2008. 154:978-993), nerve deafness (Bonny *et al.* 2005. *Rev Neurosci* 16: 57-67; Tan and Shepherd. 2006. *Am J Pathol* 169:528-543), nerve damage in the peripheral nervous system (Arnett *et al.* 2007. *Brain Res* 1183:32-42; Provenzano *et al.* 2008. *Laryngoscope* 118:87-93; Fan *et al.* 2008. *Eur J Neurosci* 27:2380-2390); damage to the central nervous system (Harrington *et al* 2004. *PNAS* 101:6226-6230; Beanie *et al.* 2002. *Neuron* 36:375-386; Domeniconi *et al.* 2007. Mol Cell Neurosci 34:271-279; Jansen *et al.* 2007. *Nat Neurosci* 10:1449-1457; Srinivasan. 2004. *J Biol Chem* 279:41839-41845), autonomic neuropathies (Al-Shawi *et al.* 2008. *Eur J Neurosci* 27:2103-2114; Jansen *et al. supra*) and schizophrenia (Lu and Martinowich. 2008. *Novartis Found Symp* 289:119-129). Thus, in the art, there is more than sufficient evidence of a nexus between apoptosis and the pro-apoptotic effect of pro-neurotrophins and the etiology, pathology and symptomology of an injury or dysfunction of the central or peripheral nervous system.

The Examiner also asserts that the specification lacks enabling support with respect to potential problems in delivery of the antibody of the claims across the blood brain barrier (BBB) and treatment of a broad scope of injuries and dysfunctions. As an initial matter, Applicants note that the Examiner has read a limitation of peripheral administration in the claims where it is not recited. In addition, antibody treatment of brain infections is indeed feasible, and the techniques were available in the art well before the filing of the instant application. *See* http://www.cdc.gov/ncidod/eid/vol2no3/casadeva.htm and the references cited therein. For example, it was known that two different types of modifications can make antibodies more easily cross the BBB. The technologies were also well known in the art before the filing of the instant application. *See* Bickel. 1995. *Adv Drug Delivery Rev* 15:53-72. One of the modifications includes altering the charge of antibody molecules for enhanced brain penetration, which is exemplified in Triguero *et al.* (1989. *PNAS* 86:4761-4765). The second modification employs the use of drugs that are able to cross the BBB and linking such drugs to antibody molecules, as

disclosed by Friden *et al.* (1991. *PNAS* 88:4471-4475) and Boado *et al.* (2007. *Bioconjugate Chem*, 18:447-455). Finally, application of antibodies against anti-amyloid antibodies to treat Alzheimer's Disease was demonstrated by Banks *et al*, (*supra*). Accordingly, it was illustrated that even without altering the charge of antibodies or coupling antibodies to drugs that cross the BBB, therapeutic antibodies are able to cross the BBS themselves and exert beneficial effects. Applicants respectfully submit that a person of skill in the art would know how to treat and administer macromolecules, including antibodies, that could pass the BBB.

In view of the foregoing, Applicant respectfully submits that the instant specification teaches those skilled in art how to make and use the full scope of the claimed invention without undue experimentation. Accordingly, the claims are fully enabled by the instant specification, and withdrawal of the rejection under this section is respectfully requested.

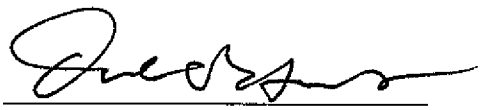
CONCLUSION

Applicants submit that the present Application is in condition for allowance and respectfully request the same. If any issues remain, the Examiner is cordially invited to contact Applicants' representative at the number provided below in order to resolve such issues promptly. Although the undersigned is not the attorney of record in this case, he hereby represents to the United States Patent and Trademark Office that he is authorized to represent Applicant pursuant to 37 CFR 1.34. *See* M.P.E.P. Section 405.

Please charge fees, including any fees for additional extension of time, or credit overpayment, to Deposit Account No. 04-0258.

Respectfully submitted,

Dated: October 14, 2008

By: 

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